Cephalosporin use in treatment of patients with penicillin allergies

Daryl D. DePestel, Michael S. Benninger, Larry Danziger, Kerry L. LaPlante, Chandler May, Allan Luskin, Michael Pichichero, and James A. Hadley

Abstract

Objective: To review the evidence that supports the use of certain cephalosporins in penicillin-allergic patients.

Data sources: Published articles were identified through Medline and EMBASE (1960–2007) using the search terms *penicillin* and *allergy* and *cephalosporin* and *cross-reactivity*. Additional sources were identified from the authors' personal collection and the reference bibliographies.

Study selection: The articles found in the search were limited to the English language and screened for relevance. Review articles and republication of results were excluded. A total of 44 articles reported evidence of cross-reactivity between cephalosporins and penicillins in human and animal studies. Additional references provided background and perspective.

Data synthesis: Physicians may now prescribe certain cephalosporins in patients with a history of a nonserious, non–life-threatening penicillin reaction. Exclusions include type I anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, and other potentially life-threatening responses to medication. Recent reports demonstrate that a considerable body of literature describing the cross-reactivity between cephalosporins and penicillin was established based on nonallergic adverse reactions or in vitro studies rather than on clinically relevant immune-mediated reactions. Oral rechallenge and skin testing data support the relationship of the beta-lactam side-chain structures of these drugs as a predictor of cross-reactivity.

Conclusion: Recent data suggest that the incidence of cross-reactivity among penicillins and cephalosporins is lower than historically reported. Pharmacists should be aware that cephalosporin cross-reactivity in a penicillin-allergic patient is not necessarily a class effect. Dispensing should be evaluated based on the type of allergic manifestations and the drug prescribed.

Keywords: Allergy information, antimicrobial agents, evidence-based medicine, antibiotics, prescription drugs, skin testing.

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Daryl D. DePestel, PharmD, is Clinical Associate Professor of Pharmacy, Department of Clinical Sciences, College of Pharmacy, and Clinical Pharmacist, Infectious Diseases, University of Michigan Hospitals and Health Centers, University of Michigan, Ann Arbor. **Michael S. Benninger, MD,** is Chairman, Head and Neck Institute, The Cleveland Clinic, Cleveland, OH. **Larry Danziger, PharmD,** is Professor of Pharmacy Practice, and Codirector, Infectious Disease Pharmacotherapy Section, College of Pharmacy, University of Illinois at Chicago. **Kerry L. LaPlante, PharmD,** is Assistant Professor, College of Pharmacy, University of Rhode Island, Kingston, and Clinical Pharmacist, Infectious Diseases, Veterans Affairs Medical Center, Providence, RI. **Chandler May, MD, JD, MS, FCLM,** is Specialist in Otolaryngology, Sinusitis, and Allergy, private practice/clinical research, Santa Barbara, CA. **Allan Luskin, MD,** is Clinical Associate Professor of Medicine, University of Wisconsin–Madison, and Director, Center for Respiratory Health, Dean Medical Center, Madison, WI. **Michael Pichichero, MD,** is Professor of Pediatrics, Medicine and Microbiology/Immunology, Department of Microbiology/Immunology, and **James A. Hadley, MD, FACS,** is Associate Professor of Otolaryngology, Department of Otolaryngology–Head and Neck Surgery, University of Rochester Medical Center, Rochester, NY.

Correspondence: Daryl D. DePestel, PharmD, University Hospital, B2D301, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-0008. Fax: 734-936-7027. E-mail: darylddd@umich.edu

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Cephalosporin antimicrobials are frequently prescribed for many common infections such as sinusitis, acute otitis media (AOM), acute exacerbations of chronic bronchitis, and pneumonia, as well as for skin and soft tissue infections. For decades, a relative contraindication to the use of cephalosporins has been in patients with a history of penicillin allergy. Reactions to penicillin in the general population are common, with approximately 10% of patients reporting a penicillin allergy. Pharmacists and other health care providers are acutely aware of the potential cross-reactivity between penicillin and cephalosporins. Until recently, the relative risk remained poorly defined in patients with "known" allergic reactions to penicillins subsequently receiving cephalosporins. However, new guidelines recommending cephalosporin use in penicillin-allergic patients and new information regarding cross-reactivity between agents with similar side-chain structures have made reexploring the issues necessary.

Objective

This article reviews the evidence supporting new recommendations that certain cephalosporins can be administered to penicillin-allergic patients. The objective is to ensure that pharmacists are aware of the basis for the paradigm change in prescribing and are able to discern between an acceptable prescription and one that requires intervention. A background of penicillin allergy and a review of the cross-reactivity evidence are presented.

At a Glance

Synopsis: Decisions on whether to dispense cephalosporins to patients with previous allergies to penicillin should be based on the type of allergic manifestations and the specific drug prescribed, according to authors of this review article. A considerable body of literature describing the cross-reactivity between cephalosporins and penicillin was established based on nonallergic adverse reactions or in vitro studies instead of clinically relevant immune-mediated reactions. Data from oral rechallenge and skin testing support the relationship of the beta-lactam side-chain structures of these drugs as a predictor of cross-reactivity. Cephalosporin cross-reactivity in penicillin-allergic patients is not necessarily a class effect.

Analysis: *Pharmacists in various practice settings regularly are presented with cephalosporin prescriptions for patients with a history of penicillin allergy. The history of the previous allergic response, drug, onset, duration, and extent must be assessed to determine the safety of starting cephalosporin therapy. Delaying or incorrectly modifying therapy can be avoided by understanding the difference between an adverse event and an allergic reaction, and national guidelines can be consulted in specific situations.*

Search criteria

Published articles were identified through Medline and EMBASE (1960–2007) using the search terms *penicillin* and *allergy* and *cephalosporin* and *cross-reactivity.* The articles found in the search were limited to the English language. Additional sources were identified from the authors' personal collection and the reference bibliographies. Articles were screened for relevance by searching specifically for cephalosporin testing in a penicillin-allergic patient. Testing included drug rechallenge by either the oral or injectable route or skin testing. Review articles and papers with previously published results were excluded. A total of 44 articles reported evidence of cross-reactivity between cephalosporins and penicillins in human and animal studies. Additional references provided background and perspective.

Current evidence-based guidelines

The respiratory treatment guidelines issued by the American Academy of Pediatrics[1–3] identify a beta-lactam as the initial drug of choice for treating nonsevere AOM and further recommend cefdinir, cefuroxime axetil, or cefpodoxime in patients with nonanaphylactic (type I) allergy to penicillin (Figure 1). Patients with a type I penicillin allergy should be given a macrolide antibiotic; cases of severe AOM should be treated with ceftriaxone. While clindamycin and other antibiotics may be active against the typical respiratory pathogens, their use is generally reserved for clinical failure in an overall effort to forestall the development of bacterial resistance. Patients exhibiting a non–type I, nonanaphylactic reaction to penicillin may still receive a cephalosporin, unless a history of a potentially serious type II, III, or IV reaction or idiopathic reaction is noted, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), interstitial nephritis, vasculitis, serum sickness, hemolytic anemia, neutropenia, or thrombocytopenia.

Guidelines developed by the Sinus Allergy Health Partnership[4] and adopted by the American Academy of Otolaryngology–Head and Neck Surgery, American Academy of Otolaryngic Allergy, and the American Rhinology Society also include antimicrobial therapy recommendations. Although separate guidelines were developed for adults and children, both focus treatment decisions on the severity of symptoms and previous antibiotic use. Similar to the American Academy of Pediatrics guidelines, the Sinus Allergy Health Partnership guidelines recommend penicillins and cephalosporins as first-line treatment options except in cases of true beta-lactam allergy, such as type I reactions. Non–type I, nonanaphylactic but life-threatening reactions, such as SJS, TEN, interstitial nephritis, vasculitis, serum sickness, hemolytic anemia, neutropenia, and thrombocytopenia, also represent

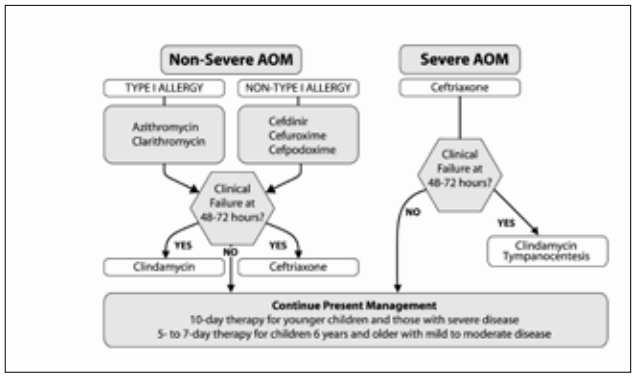

Figure 1. American Academy of Pediatrics–recommended antibacterial agents for patients with allergy to penicillin in the management of AOM

Abbreviation used: AOM, acute otitis media.

absolute contraindications to the readministration of any beta-lactam antibiotic.

Defining and redefining allergic reactions

The common method for characterizing adverse drug reactions (ADRs) is to separate them first into immunologic and nonimmunologic reactions. Nonimmunologic reactions include predictable adverse effect and toxicity states. Idiosyncratic reactions are typically nonimmunologic, but as more information has become available regarding drug metabolism and pharmacogenomics, many idiosyncratic reactions have been repositioned in the toxicity or adverse effect subcategories. Anaphylactoid reactions presenting with anaphylactic-like symptoms, but without evidence of immunologic sensitization, are also classified as nonimmunologic.

The immunologic reactions are subdivided into types I, II, III, and IV reactions and idiopathic reactions, with the latter sometimes referred to as type V.[5] Type I or immediate/accelerated reactions typically occur within 1 hour (immediate) or develop within 1 to 72 hours (accelerated) after the initial exposure to penicillin. Type I allergy is confirmed when antibiotic-specific immunoglobulin (Ig)E antibodies are detected in the serum. Separately considered are other serious type II, III, or IV reactions or idiopathic reactions, such as SJS, TEN, interstitial nephritis, vasculitis, serum sickness, hemolytic anemia, neutropenia, and thrombocytopenia.

Late reactions, also referred to as type II, III, and IV ADRs, tend to occur after 72 hours. Type II and III reactions may be mediated by IgG and complement or IgG and IgM immune complexes, respectively, but do not involve IgE. These reactions may occur at any time during therapy. Clinical signs of type II and III reactions include an increase in the clearance of erythrocytes and platelets by the lymphoreticular system, serum sickness, drug fever, or tissue injury. Type IV reactions include contact dermatitis, maculopapular rashes or morbilliform rashes. When a patient has experienced a rash from a penicillin or cephalosporin, an inquiry as to the onset, character, and duration can provide valuable clues to type the adverse reaction.

Although far less common than nonimmunologic reactions, type I reactions are the most clinically important because of their potentially cataclysmic and catastrophic nature. Such a reaction occurs when the body produces an IgE antibody directed against an antigen (foreign protein; i.e., the parent drug or its metabolite). The sequence of events begins when the antimicrobial, functioning as an allergen, is presented to an antigen-presenting cell. A T-cell–dependent release of cytokines, particularly B-cell–inducing cytokines, such as interleukin (IL)-4 and -13, activates a specific IgE type B-cell that evolves into a plasma cell, which in turn produces serum-specific IgE (Figure 2). The IgE then circulates several days before fixing to mast cells and basophils. On subsequent reexposure, the allergen (drug) will result in the binding of two neighboring IgE molecules with the same specificity, activating the mast cells to release a variety of very potent vasoactive and proinflammatory (preformed or rapidly formed) mediators. These mediators result in the classic immediate (within minutes) onset of the signs and symptoms of anaphylaxis: wheezing, sneezing, swelling of the larynx, urticaria, pruritis, bronchospasm, and hypotension.

Immediately released (preformed) mediators include histamine and, to a lesser extent, tumor necrosis factor-alpha, proteases, and heparin. Rapidly formed mediators are typically lipid derived and include prostaglandins and cysteinyl leukotrienes.[6] The immediate-release reaction may occur during a prolonged first exposure or with a second later exposure. The length of time to sensitization is variable, making the reaction time unpredictable. Sensitivity may occur after a long period of apparent lack of sensitivity and tolerance to multiple exposures to a given drug.

A late-phase reaction that is predominantly inflammatory also occurs hours after the immediate acute-phase reaction and leads to a variety of upper- and lower-airway and cardiovascular

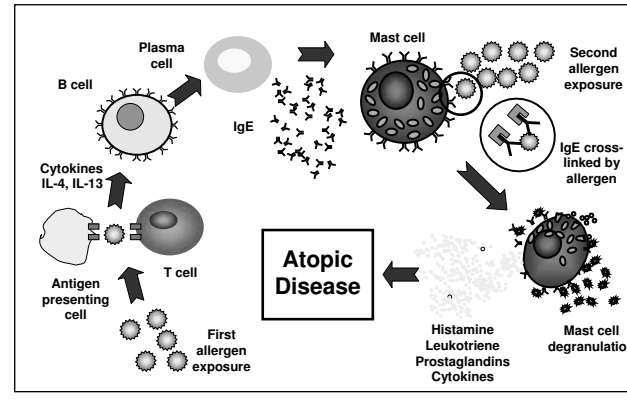

Figure 2. Overview of the IgE-mediated inflammatory cascade

Abbreviations used: IgE, immunoglobulin E; IL, interleukin.

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symptoms. This late-phase reaction is mediated by (1) cytokines and chemokines, including IL-4 and -13, and (2) a recruitment of inflammatory cells, predominantly eosinophils and, to a lesser extent, activated lymphocytes. A clinically important late-phase reaction occurs in about 25% of patients who experience a major immediate reaction.

Clinical drug treatment is predominantly directed at the immediate reaction and primarily mediated by histamines, prostaglandins, and leukotrienes. Within minutes to hours, the immediate-release mediators produce bronchoconstriction, sneezing, mucous production, itching, and hives. As previously discussed, the immediate-release reaction may lead to vascular dilatation, edema, and cardiogenic shock.

Contemporary categorization of ADRs

With improved understanding of their pathophysiologic and clinical manifestations, categorization of ADRs, as previously described by Gell and Coombs,[5] has been redefined. ADRs may now be categorized as type A and B reactions. Type A reactions are the most common, frequent, and predictable and include nonimmunologic reactions, whereas type B reactions include the less common, more serious, and less predictable immunologic reactions, as well as the idiosyncratic reactions. At least 75% of ADRs are type A reactions, which include adverse effects and toxicities related to the pharmacologic action of the drug.

As previously mentioned, type B reactions are subdivided into two groups: immunologic (including IgE-mediated) and idiosyncratic. In contrast to immunologic reactions, idiosyncratic reactions have no identifiable immunologic sensitivity. There are three principle types: anaphylactoid, drug metabolism, and haptenation without metabolism.

Anaphylactoid reactions are clinically indistinguishable from anaphylaxis, but no IgE involvement can be identified; these may occur through the direct action of a drug on mast cells or other mediator-releasing cells. One example is activation of the complement pathway, resulting in the production of anaphylatoxins C3A and C5A. The latter act either directly or indirectly on mast cells to cause mediator release without involving IgE. This is likely the mechanism witnessed in severe radiographic contrast media reactions. Anaphylactoid reactions may also occur when a drug directly activates mediator-releasing cells. The itching and hives associated with opiates are likely a direct action on mast cells not involving IgE. Another example is the anaphylactic-like events in some patients on nonsteroidal anti-inflammatory agents that act to preferentially produce lipooxygenase products.

Idiosyncratic reactions that involve drug metabolism occur most commonly at any of three different phases of metabolism: bioactivation (typically by the cytochrome system), glucuronidation, and acetylation. ADRs tend to occur when bioactivation exceeds detoxification and may be related to a genetic polymorphism (a trait that has differential expression in >1% of the population) in drug-metabolizing enzymes.[7] The metabolism of sulfonamides provide one example. In the usual case, acetylation of the compound results in excretion. However, if the drug is preferentially oxidized rather than undergoing acetylation, it may be either excreted or, alternatively, haptenized to *N*-4-sulfonamidoyl hapten, which is more highly reactive. Certain conditions appear to drive the oxidation pathway, such as infectious diseases associated with cytomegalovirus or the human immunodeficiency virus. This may explain, in part, why more sulfonamide allergies are reported in a higher frequency in these subpopulations of patients with infection.

The third type of idiosyncratic reaction is haptenation without drug metabolism. Chemical structural characteristics of the parent drug allow binding with host proteins to form haptens. By definition, haptens are incomplete or partial antigens capable of binding with specific antibodies but, in and of themselves, are incapable of simulating additional antibody production. Haptenation without metabolism can occur with penicillins to elicit an allergic response.

Assessing an allergic reaction

A major difficulty in assessing allergy is the current lack of clinically valuable diagnostic (in vitro or in vivo) tests. T-cell–related tests correlate fairly well with drug rashes but are not clinically available. Immediate skin tests for amoxicillin and penicillin have a poor positive predictive value (sensitivity) but excellent negative predictive value (specificity). Penicilloyl-polylysine skin testing, used for decades but not marketed currently, can establish IgE sensitivity to the major metabolite of penicillin; the Food and Drug Administration is currently reviewing an application for marketing a device for this purpose. The in vitro allergen-specific IgE antibody, or radioallergosorbent, test is not clinically reliable as an index for immediate penicillin hypersensitivity.

The diagnostic algorithm used to investigate an ADR includes a review of the medical history, nature of the event, timing, onset, course, current medications, and previous ADRs and outcomes. In general, 75% of ADRs are predictable (type A). The IgE-mediated (type B) immunologic drug reactions occur in a small percentage of patients. Symptoms do not resemble the pharmacologic action of the drug but rather a known immunologic response. Readministering a drug is generally contraindicated in an IgE-mediated (type I) reaction given the risk of a similar, or perhaps more severe, allergic reaction.

Desensitization, either orally or intravenously, is associated with a 90% to 95% success rate in documented IgE-mediated (type I) sensitivity, particularly to penicillin, and can be used to permit safe administration of the drug in a patient with a compelling reason. This technique is not without substantial risk and must be performed in a highly controlled setting by trained clinicians. If the patient history is inconclusive and considered an idiosyncratic (non–IgE-mediated) type B reaction, then desensitization or graded-dose challenge (giving small increasing amounts of drug over a period of a few hours to days

to weeks) may be considered and is often successful. An exception lies in nonanaphylactic but life-threatening reactions such as SJS or TEN. SJS and TEN are considered a continuum of the same disease and represent absolute contraindications to readministration of the offending agent. Reactions are often more severe upon subsequent drug exposure and are not predictable by in vitro or in vivo testing.

Structural similarities between beta-lactam antibiotics

Cephalosporins are a class of semisynthetic antimicrobial drugs related to the structure and activity of penicillin. As with many antibiotics, cephalosporins were discovered from natural sources. Thirty-two different cephalosporin compounds have been developed since the initial isolation of cephalosporin C off the coast of Sardinia in 1948. Several were never marketed; others are no longer commercially available (Table 1). Subcategorization of cephalosporins into four different generations was based on their development by industry; however, in general, each subsequent generation has a broader spectrum of activity against gram-negative organisms while maintaining or losing its activity against gram-positive organisms.

Beta-lactam antibiotics include penicillins, cephalosporins, carbapenems, monobactams, and beta-lactam/beta-lactamase inhibitors. These compounds all possess a characteristic beta-lactam ring. When the beta-lactam ring is fused to a 5-membered thiazolidine ring, or penam, the drug is classified as a penicillin (Figure 3). When fused to a 6-membered dihydrothiazine ring, or cephem, it is classified as a cephalosporin (Figure 4). Penams (penicillins) are different from penems, such as imipenem and meropenem, which have the same general beta-lactam structure but contain a carbon double bond in the attached 5-membered ring.[8]

Although both penicillins and cephalosporins may incorporate different salt forms at the ester binding site, penicillins have only one side chain (6-position) while cephalosporins have two side chains (7- and 3-position). The side chains differentiate the activity and metabolic parameters of individual drugs within each class. Substitution at the 6-position side chain of penicillins generally results in increased potency. With cephalosporins, substitutions at the 7-position side chain alter the microbiologic activity of the drug. Modifying cephalosporin molecules at the 3-position predominately affects changes in pharmacokinetic parameters, particularly drug metabolism. The penicillin 6-position and cephalosporin 7-position side chains with an acylamino structure have demonstrated parallel function.

Cephalosporin allergy and cross-reactivity in penicillin allergy

Hypersensitivity reactions are among the most serious systemic reactions caused by cephalosporins. The relative risk of an anaphylactic reaction to cephalosporins ranges from 1:1,000 to 1:1,000,000.[9–11] This risk is increased by a factor of four in patients with a history of penicillin allergy.[12,13]

The most serious adverse reaction of the penicillins is a type I IgE-mediated hypersensitivity reaction, or anaphylaxis. Penicillins are capable of acting as haptens to combine with human proteins. Once sensitized with a hapten-carrier complex, the patient can manifest an allergic reaction to penicillin. Penicilloyl and penicillanic acid—byproducts formed when the beta-lactam ring is opened—are considered the major determinants of penicillin allergy. These byproducts allow nitrogen from the beta-lactam ring to form an amide linkage to body proteins. Benzylpenicillin and sodium benzylpenicilloate, called the minor determinants, are produced by drug degradation in the gastrointestinal tract and metabolism. Both the major and minor determinants may be involved in anaphylactic or urticarial reactions. Cephalosporins are also suspected to form haptens,

Table 1. Cephalosporins by generation

First generation	Second generation	Third generation	Fourth generation
Cefadroxil	Cefaclor	Cefdinir	Cefepime
Cefatrizine	Cefamandole	Cefetamet	Cefpirome
Cefazolin	Cefmetazole	Cefixime	
Cephalexin	Cefonicid	Cefoperazone	
Cephaloridine	Cefotetan	Cefotaxime	
Cephalothin	Cefoxitin	Cefotiam	
Cephapirin	Cefprozil	Cefpodoxime	
Cephradine	Cefuroxime	Cefsulodin	
	Loracarbef	Ceftazidime	
		Ceftibuten	
		Ceftizoxime	
		Ceftriaxone	
		Moxalactam	

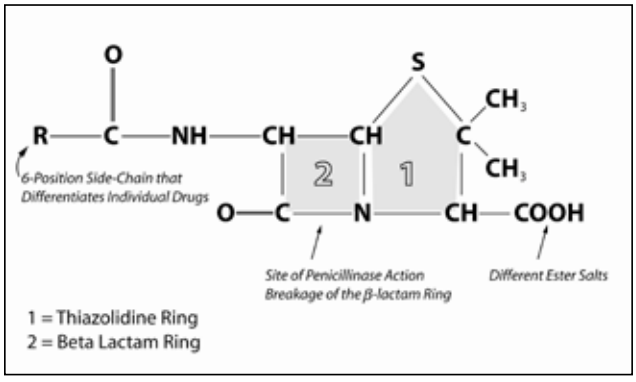

Figure 3. Chemical structure of penicillin

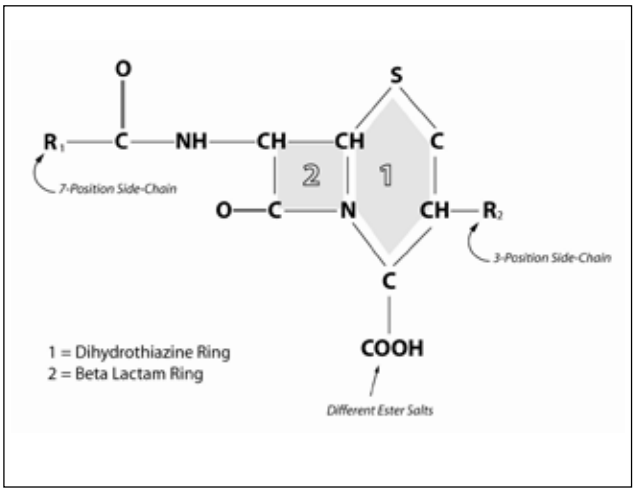

Figure 4. Chemical structure of cephalosporins

although the specific chemical byproducts remain unknown. In theory, the number of potential haptens with cephalosporins is quite large, whereas both the 7- and 3-position side chains may be involved.

The frequency of cephalosporin cross-reactivity in a penicillin-allergic patient is reported to range anywhere from 7% to 18% of patients.[9] The actual incidence rate was confounded in the early literature by nonallergic ADRs being reported as drug allergy.[14] In addition, the manufacturing process of penicillins and cephalosporins has been refined over time. Until the mid-1980s, many penicillins were produced by fermentation from a cephalosporin mold and not from a penicillin mold. The drugs were thereafter synthetically modified to create the penicillin structure but were contaminated with cephalosporin-type products until approximately 1985. With improvements in the manufacturing process, more cross-reactivity exists currently among cephalosporins than between cephalosporins and penicillins.

Several studies have reported the incidence of urticaria and rashes from penicillins and cephalosporins. Ampicillin has a 5.6% rate of rash reported,[15] while the reaction rate of urticaria from amoxicillin was reported at 0.8%.[16] The rate of rashes from cephalosporins ranges from less than 1.0% to 3%, depending on the individual drug.[10,16–18]

Cross-reactivity to beta-lactam antibiotics

Although not currently feasible with commercially available products, skin testing has been used by researchers to more accurately verify the incidence of cephalosporin cross-reactivity in pencillin-allergic patients. Penicillin skin tests are performed using a mixture of penicillin G, the major determinant of penicilloyl-polylysine, a minor determinant mixture of benzylpenicillin, and/or ampicillin.[19] Such tests have a positive predictive value of less than 20% upon initial administration[11,12,20] and approximately 60% with rechallenge.[21–23] While the sensitivity is lacking, penicillin skin tests have a negative predictive value or specificity between 97% and 99%. A patient with a negative skin test has a 3% or lower chance of having an immediate allergic reaction.

When skin testing is used to confirm penicillin allergy, only the first-generation cephalosporins cause noteworthy cross-reactivity. These data suggest that the cephalosporin cross-reactivity rate may be lower than that seen between penicillins and other classes of antibiotics.[24] While cross-reactivity reactions may occur with first-generation cephalosporins, changes in the chemical structure of most cephalosporins that are second generation and higher make them less similar to penicillin.[25]

Side chains have been investigated as a link to cross-allergenicity between drugs and among drug classes. One of the first animal studies to investigate cross-allergenicity between penicillins and cephalosporins reported that the side chain played an unimportant role.[26] However, since 1962, a growing body of evidence suggests otherwise.[27–30] In 1990, Nagakura et al.,[31] using monoclonal antibody technology, found that both the 3- and 7-position cephalosporin side chains and a new antigenic determinant (formed by conjugation of the beta-lactam ring with a carrier protein) elicited an immune response to skin testing. Mayorga et al.[32] subsequently reported that 92% of the antibodies recognized an epitope in which the side chain was the major constituent.

Side-chain structure has been used to regroup the penicillins and cephalosporins, underscoring their potential for cross-allergenicity.[25] Drugs with similar 6- or 7-position side chains may exhibit cross-allergenicity with each other, just as drugs with similar 3-position side-chain structures may exhibit cross-reactivity. Figure 5 is a matrix of penicillin and cephalosporins illustrating side-chain similarities. Each number in the matrix indicates side-chain similarity between two drugs. Cross-allergenicity is expected between each similar pair. For example, a patient allergic to amoxicillin would very likely manifest an allergic reaction to ampicillin, cefaclor, cefadroxil, cefatrizine, cefprozil, cephalexin, and cephradine. However, the patient would not be expected to exhibit an allergic response to cefa-

	Amoxicillin	Ampicillin	Cefaclor	Cefadroxil	Cefamandole	Cefatrizine	Cefdinir	Cefepime	Cefetamet	Cefixime	Cefmetazole	Cefoperazone	Cefotaxime	Cefotetan	Cefoxitin	Cefpirome	Cefpodoxime	Cefprozil	Cefsulodin	Ceftazidime	Cefteram
Amoxicillin		6	6/7	6/7		6/7												6/7			
Ampicillin	6		6/7	6/7		6/7												6/7			
Cefaclor	6/7	6/7		7		7												7			
Cefadroxil	6/7	6/7	7			7												7			
Cefamandole											3	3		3							
Cefatrizine	6/7	6/7	7	7														7			
Cefdinir										3											
Cefepime									7				7			7	7				7
Cefetamet								7					7			7	7				7
Cefixime							3														
Cefmetazole					3							3		3							
Cefoperazone					3						3			3							
Cefotaxime								7	7							7	7				7
Cefotetan					3						3	3									
Cefoxitin																					
Cefpirome								7	7				7				7				7
Cefpodoxime								7	7				7			7					7
Cefprozil	6/7	6/7	7	7		7															
Cefsulodin																				3	
Ceftazidime																			3		
Cefteram								7	7				7			7	7				
Ceftibuten																					
Ceftizoxime								7	7				7			7	7				7
Ceftriaxone								7	7				7			7	7				7
Cefuroxime															3						
Cephalexin	6/7	6/7	7	3,7		7												7			
Cephaloridine															7						
Cephalothin													3		7						
Cephapirin													3								
Cephradine	6/7	6/7	7	3,7		7												7			
Penicillin G															6/7						

Figure 5. Matrix of penicillin and cephalosporin drugs with similar side-chain structures

3, similarity at the cephalosporin 3–position side chain; 7, similarity at the cephalosporin 7–position side chain; 6/7, similarity at the penicillin 6–position side chain and the cephalosporin 7–position side chain.

Drugs with 3-position or 7-position side chains dissimilar than any other include cefazolin, cefonicid, cefotiam, and moxalactam.

mandole, cefdinir, cefepime, etc., unless he/she was also allergic to another cephalosporin or penicillin with a similar side chain to the reference drug. In a similar analysis, cefamandole would not be given to a patient who was allergic to cefmetazole, cefoperazone, or cefotetan. Likewise, cefdinir would not be given to a patient allergic to cefixime. All but four drugs (cefazolin, cefonicid, cefotiam, and moxalactam) share a structural relationship with another drug.

Comparative cross-reactivity, on the basis of skin test results, has been reported in several publications.[21–23,25,30,33–48] The sample size is small in some of the earlier studies; however, the results consistently support the side-chain model. Oral

Ceftibuten	Ceftizoxime	Ceftriaxone	Cefuroxime	Cephalexin	Cephaloridine	Cephalothin	Cephapirin	Cephradine	Penicillin G
				6/7				6/7	
				6/7				6/7	
				7				7	
				3,7				3,7	
				7				7	
	7	7							
	7	7							
	7	7				3	3		
			3		7	7			6/7
	7	7							
	7	7							
				7				7	
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						7			6/7
					7		3		6/7
						3			
				3,7					
					6/7	6/7			

rechallenge studies have examined 5,420 patients with a history of penicillin who received cephalosporins and found that 2.55% had a reaction to a cephalosporin.[21–23,25,34,38,39,42–44,46,48–62] The majority of cross-reactivity reactions occurred after a first-generation cephalosporin with a side chain similar to penicillin and amoxicillin was administered.

The structural relationship of cross-reactivity between cephalosporins was recently reported in a case of allergy to cefuroxime axetil.[63] Allergy was confirmed 4 weeks after the incident using prick test and intradermal test. Cross-allergenicity was evaluated in the same way using a variety of different cephalosporins and penicillins. Positive prick test results were seen with ceftriaxone and cefotaxime; positive intradermal test results were observed with ceftriaxone, cefotaxime, cefepime, and oxacillin. The author implicated a common methoxyimine substructure in the side chain of each of these drugs as contributing to the results. However, only one-half of the side-chain structure has been taken into account. The side chain of cefotaxime, ceftriaxone, and cefepime includes both a methoxyimine group and a sulfidine aniline group. In the case of cefuroxime, the side chain includes the methoxyimine group plus a furan. The coincidence between side-chain substructure and cross-reactivity has not been fully investigated but may be an area of continued research, as demonstrated by this case.

Apter et al.[64] calculated the unadjusted risk ratio of penicillin–cephalosporin cross-reactivity in a retrospective review of 534,810 patients who received penicillin followed by, at least 60 days later, cephalosporin. The authors documented allergic-like events (ALEs) occurring within 30 days of dosing, including anaphylaxis, urticaria, angioedema, erythema multiforme, laryngeal spasm, drug-induced dermatitis, TEN, bronchospasm, asthma, eczema, and ADRs. A total of 3,877 patients had an ALE following penicillin but only 43 (1.1%) experienced a second ALE after receiving a cephalosporin (unadjusted risk ratio 10.0 [95% CI 7.4–13.6]). In a separate analysis reviewing sulfonamide antibiotics, 1.6% of penicillin-sensitive patients experienced a second ALE after receiving a sulfonamide (7.2 [3.8–12.5]).

Legal implications

When cephalosporins were first introduced to the market, they were indicated for use in penicillin-allergic patients. Given the subsequent acknowledgement of adverse events related to cross-reactivity, the labeling changed several times. The package insert for most cephalosporins currently states, "Cross-hypersensitivity among the β-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with penicillin allergy." This generalized rate of reaction has been redefined to 1.1% or lower through an understanding of the distinction between penicillin allergy and nonallergic adverse reactions, skin testing data, the importance of the side-chain structure, and the recent physician guidelines supporting use of certain cephalosporins for treating respiratory infections in patients with non–type I penicillin allergy. Science now recognizes the unique side chains as a major source of cross-reactivity (structural activity relationship), replacing the concept of a class effect.[63,64]

The legal implications of using a cephalosporin in a penicillin-allergic patient should reflect the understanding that package inserts regarding cross-reactivity contain outdated information. Medical malpractice falls under civil law and is partially defined as a breach of the duty of care owed by the physician or health care provider. The responsibility of a pharmacist

who dispenses a prescription to a patient with a known allergy falls within the scope of this definition. Adhering to the labeled package insert precautions and not dispensing a cephalosporin to patients with a history of penicillin allergy is a conservative approach but fails to recognize recent scientific data and contemporary physician guidelines.

The 1998 landmark legal case *Morlino v Medical Center of Ocean County* resolved the issue of whether the package insert alone could establish the standard of care or negligence. Ms. Morlino, 8 months pregnant, was treated for acute pharyngitis with amoxicillin on March 5, 1990. Fifteen days later, she presented to the emergency department after failing her course of therapy. A throat culture grew *Haemophilus influenza* resistant to ampicillin, cephalosporin, erythromycin, clindamycin, nafcillin, and penicillin. The physician considered ciprofloxacin, a fluoroquinolone, as possible therapy. Upon consulting the *Physicians' Desk Reference (PDR)*, the physician noted a warning regarding the use of ciprofloxacin in children or pregnant women. The warning stated, "Histopathological examination of the weight-bearing joints of dogs has revealed permanent lesions of the cartilage. Risk cannot be ruled out. Human studies are lacking and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk." As such, ciprofloxacin is rated for use in pregnancy as Category C.

After the alternatives were considered, Ms. Morlino was given oral ciprofloxacin 500 mg at 12:30 a.m. on March 21 and discharged 10 minutes later. She soon began to feel dizzy, weak, and short of breath. Her eyesight was blurred and she lost consciousness for several hours. Ms. Morlino was diagnosed with anaphylaxis to ciprofloxacin, and, although she survived the incident, the fetus was lost.

A medical malpractice suit for negligence was subsequently filed against the physician focusing on the *PDR* and package insert warning against using ciprofloxacin in pregnancy. The case was ultimately appealed to the New Jersey Supreme Court to determine if the *PDR* or product labeling alone could establish the standard of care or negligence. The court found that product labeling and parallel *PDR* references alone do not establish a standard of care but are allowed into evidence provided expert testimony is also presented to explain the standard to the jury.

In the context of dispensing a cephalosporin to a patient with a history of penicillin allergy, the American Academy of Allergy, Asthma & Immunology (AAAAI) issued an updated practice parameter in 2005 for diagnosing and managing anaphylaxis.[66] These guidelines have been further refined in a 2007 supplement on risk assessment in anaphylaxis.[67] The AAAAI parameter states that penicillin is the most common cause of drug-induced anaphylaxis. Given that penicillin spontaneously degrades to major and minor antigenic determinants, the value of skin testing with reagents on this basis yields negative results in approximately 90% of patients with a history of penicillin allergy (97–99% specificity for IgE reactions). Although

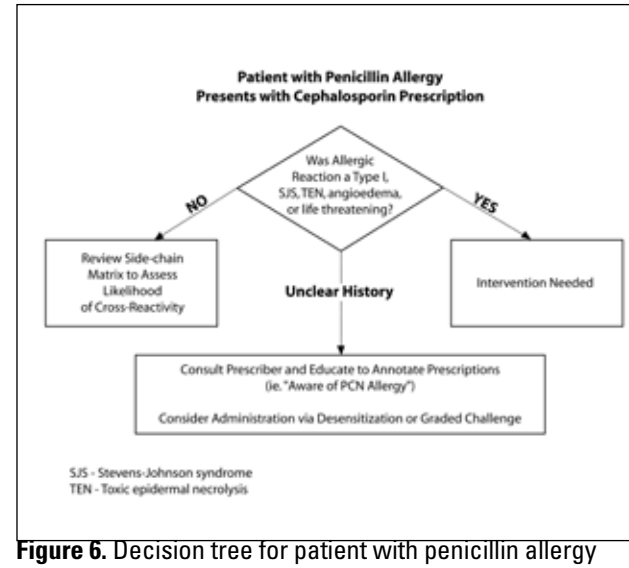

Figure 6. Decision tree for patient with penicillin allergy presenting with cephalosporin prescription

the extent of allergic cross-reactivity between penicillin and cephalosporins is unknown and appears to be low, about 4% of patients with a proven penicillin allergy (by skin testing) also react to cephalosporins. Patients with a history of penicillin allergy who have negative penicillin skin test responses might safely receive cephalosporins. The AAAAI recommends that patients with a positive penicillin skin test (1) receive a non–beta-lactam antibiotic, (2) receive a cephalosporin through graded challenge, or (3) undergo rapid desensitization before receiving a cephalosporin. The clinical availability of skin test reagents would provide considerable assistance in evaluating patients with a history suggesting an IgE-type adverse drug response.

When current clinical data are combined with structural activity relationship side-chain analysis, it appears that, for select cephalosporins without side-chain similarities, the relative risk of prescribing these antibiotics in a non–IgE-mediated penicillin-allergic patient is no greater than the low inherent allergic risk of the products themselves.

Conclusion

Pharmacists in various settings, including those in community pharmacy, can expect to see cephalosporin prescriptions for patients with a history of penicillin allergy. With respect to respiratory tract infections, oral cefdinir, cefuroxime axetil, or cefpodoxime are recommended for use in patients with nonanaphylactic (type I) allergy to penicillin. The side-chain theory of cross-allergenicity is supported by a considerable body of evidence and has the potential to assist the pharmacist in screening prescriptions. Referencing the matrix of side-chain similarities can help the pharmacist determine the likelihood of eliciting an adverse reaction if a cephalosporin is administered to a patient

with nonsevere penicillin allergy (Figure 6). Assessing the allergy nature, drug, onset, duration, and extent is essential to determining the safety of starting cephalosporin therapy. If the penicillin allergy is severe or life threatening, the reaction may be related to haptenation rather than the side chain and intervention is needed. Desensitization or graded challenge may be more appropriate if the allergy history is unclear. Physicians should be educated to acknowledge their awareness of the non–IgE-mediated/nonserious allergic reaction with a note on the prescription: "Aware of PCN Allergy." Cephalosporins with dissimilar side chains can be prescribed in patients not previously exhibiting a type I allergic response or a life-threatening late-onset reaction such as SJS or TEN. Understanding the difference between an adverse event and an allergic reaction may prevent delaying therapy or mistakenly changing therapy because of a lack of awareness.

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References

1. American Academy of Pediatrics, Subcommittee on Management of Sinusitis and Committee on Quality Improvement. Clinical practice guidelines: management of sinusitis. Pediatrics. 2001;108:798–808 [erratum in Pediatrics. 2001;108:A24; Pediatrics. 2002;109:40.]
2. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Follow-up management of children with tympanostomy tubes. Pediatrics. 2002;109:328–9.
3. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatrics. 2004;113:1451–65.
4. Anon JB, Jacobs MR, Poole MD, et al. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg. 2004;130:1–45.
5. Gell PGH, Coombs RRA. Classification of allergic reactions underlying disease. In: Clinical aspects of immunology. Philadelphia: F.A. Davis; 1963:317–37.
6. Shulman ES. Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. Am J Respir Crit Care Med. 2001;164:S6–11.
7. Daly AK. Pharmacogenetics of the cytochromes P450. Curr Top Med Chem. 2004;4:1733–44.
8. Dalhoff A, Janjic N, Echols R. Redefining penems. Biochem Pharmacol. 2006;71:1085–95.
9. Kelkar PS, Li JT. Cephalosporin allergy. N Engl J Med. 2001;345:804–9.
10. Platt R. Adverse effects of third-generation cephalosporins. J Antimicrob Chemother. 1982;10(suppl C):135–40.
11. Gadde J, Spence M, Wheeler B, Adkinson NF Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. JAMA. 1993;270:2456–63.
12. Lin RY. A perspective on penicillin allergy. Arch Intern Med. 1992;152:930–7.
13. Petz LD. Immunologic reactions of humans to cephalosporins. Postgrad Med J. 1971;47(suppl):64–9.
14. Robinson JL, Hameed T, Carr S. Practical aspects of choosing an antibiotic for patients with a reported allergy to an antibiotic. Clin Infect Dis. 2002;35:26–31.
15. Arndt KA, Jick H. Rates of cutaneous reactions to drugs: a report from the Boston Collaborative Drug Surveillance Program. JAMA. 1976;235:918–23.
16. Levine LR. Quantitative comparison of adverse reactions to cefaclor vs. amoxicillin in a surveillance study. Pediatr Infect Dis. 1985;4:358–61.
17. Sanders CV, Greenberg RN, Marier RL. Cefamandole and cefoxitin. Ann Intern Med. 1985;103:70–8.
18. Norrby SR. Side effects of cephalosporins. Drugs. 1987;34(suppl 2):105–20.
19. Forrest D, Schellenber R, Their VV, et al. Introduction of a practice guideline for penicillin skin testing improves the appropriateness of antibiotic therapy. Clin Infect Dis. 2001;32:1686–90.
20. Silviu-Dan F, McPhillips S, Warrington RJ. The frequency of skin test reactions to side-chain penicillin determinants. J Allergy Clin Immunol. 1993;91:694–701.
21. Solley GO, Gleich GJ, Van Dellen RG. Penicillin allergy: clinical experience with a battery of skin-test reagents. J Allergy Clin Immunol. 1982;69:238–44.
22. Sullivan TJ, Wedner HJ, Shatz GS, et al. Skin testing to detect penicillin allergy. J Allergy Clin Immunol. 1981;68:171–80.
23. Warrington RJ, Tse KS, Gorski BA, et al. Diagnosis of penicillin allergy by skin testing: the Manitoba experience. Can Med Assoc J. 1978;118:787–91.
24. Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy. 1998;18:515–40.
25. Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. Pediatrics. 2005;115:1048–57.
26. De Weck AL, Schneider CH, Gutersohn J. The role of penicilloylated protein impurities, penicillin polymers and dimers in penicillin allergy. Int Arch Allergy Appl Immunol. 1968;33:535–67.
27. Batchelor FR, Dewdney JM, Weston RD, Wheeler AW. The immunogenicity of cephalosporin derivatives and their cross-reaction with penicillin. Immunology. 1966;10:21–33.
28. Shibata K, Atsumi T, Horiuchi Y, Mashimo K. Immunological cross-reactivities of cephalothin and its related compounds with benzylpenicillin (penicillin G). Nature. 1966;212:419–20.
29. Hamilton-Miller JM, Abraham EP. Specificities of haemagglutinating antibodies evoked by members of the cephalosporin C family and benzylpenicillin. Biochem J. 1971;123:183–90.
30. Petersen BH, Graham J. Immunologic cross-reactivity of cephalexin and penicillin. J Lab Clin Med. 1974;83:860–70.
31. Nagakura N, Shimizu T, Masuzawa T, Yanagihara Y. Anti-cephalexin monoclonal antibodies and their cross-reactivities

to cephems and penams. Int Arch Allergy Appl Immunol. 1990;93:126–32.

32. Mayorga C, Obispo T, Jimena L, et al. Epitope mapping of beta-lactam antibiotics with the use of monoclonal antibodies. Toxicology. 1995;97:225–34.
33. Stewart GT. Cross-allergenicity of penicillin G and related substances. Lancet. 1962;1:509–10.
34. Thoburn R, Johnson JE 3rd, Cluff LE. Studies on the epidemiology of adverse drug reactions. IV. The relationship of cephalothin and penicillin allergy. JAMA. 1966;198:345–8.
35. Greico M. Cross allergencitiy of the penicillins and cephalosporins. Arch Intern Med. 1967;119:141–6.
36. Pedersen-Bjergaard J. Significance of the penicilloyl radical in penicillin allergy. Acta Allergol. 1967;22:466–84.
37. Girard JP. Common antigenic determinants of penicillin G, ampicillin and the cephalosporins demonstrated in men. Int Arch Allergy Appl Immunol. 1968;33:428–38.
38. Assem ES, Vickers MR. Tests for penicillin allergy in man. II. The immunological cross-reaction between penicillins and cephalosporins. Immunology. 1974;27:255–69.
39. Martin JA, Igea JM, Fraj J, et al. Allergy to amoxicillin in patients who tolerated benzylpenicillin, aztreonam, and ceftazidime. Clin Infect Dis. 1992;14:592–3.
40. Igea JM, Fraj J, Davila I, et al. Allergy to cefazolin: study of in vivo cross reactivity with other betalactams. Ann Allergy. 1992;68:515–9.
41. Vega JM, Blanca M, Garcia JJ, et al. Immediate allergic reactions to amoxicillin. Allergy. 1994;49:317–22.
42. Audicana M, Bernaola G, Urrutia I, et al. Allergic reactions to betalactams: studies in a group of patients allergic to penicillin and evaluation of cross-reactivity with cephalosporin. Allergy. 1994;49:108–13.
43. Miranda A, Blanca M, Vega JM, et al. Cross-reactivity between a penicillin and a cephalosporin with the same side chain. J Allergy Clin Immunol. 1996;98:671–7.
44. Sastre J, Quijano LD, Novalbos A, et al. Clinical cross-reactivity between amoxicillin and cephadroxil in patients allergic to amoxicillin and with good tolerance of penicillin. Allergy. 1996;51:383–6.
45. Roman A, Quarantino D, Venuti A, et al. Selective type-1 hypersensitivity to cefuroxime. J Allergy Clin Immunol. 1998;101:564–5.
46. Blanca M, Fernandez J, Miranda A, et al. Cross-reactivity between penicillins and cephalosporins: clinical and immunologic studies. J Allergy Clin Immunol. 1989;83:381–5.
47. Romano A, Mayorga C, Torres MJ, et al. Immediate allergic reactions to cephalosporins: cross-reactivity and selective responses. J Allergy Clin Immunol. 2000;106:1177–83.
48. Novalbos A, Sastre J, Cuesta J, et al. Lack of allergic cross-reactivity to cephalosporins among patients allergic to penicillins. Clin Exp Allergy. 2001;31:438–43.
49. Anne S, Reisman R. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. Ann Allergy Asthma Immunol. 1995;74:167–70.
50. Apicella M, Perkins R, Salsaw S. Cephaloridine treatment of bacterial infections. Am J Med Sci. 1966;251:266–76.
51. Dash C. Penicillin allergy and the cephalosporins. J Antimicrob Chemother. 1975;1(3 suppl):107–18.
52. Daulat S, Solensky R, Earl H, et al. Safety of cephalosporin administration to patients with histories of penicillin allergy. J Allergy Clin Immunol. 2004;113:1220–2.
53. Goodman E, Morgan M, Johnson PA, et al. Cephalosporins can be given to penicillin-allergic patients who do not exhibit an anaphylactic response. J Clin Anesth. 2001;13:561–4.
54. Griffith R, Black H. Cephalothi: a new antibiotic: preliminary clinical and laboratory studies. JAMA. 1964;189:823–8.
55. Marks J, Garrett R. Cephalexin in general practice. Post Grad Med J. 1970;46(suppl):113–7.
56. Pichichero M, Pichichero D. Selecting skin testing reagents to predict amoxicillin and cephalosporin allergy. Pediatr Asthma Allergy Immunol. 1997;11:79–93.
57. Romano A, Gueant-Rodriguez RM, Viola M, et al. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. Ann Intern Med. 2004;141:16–22.
58. Saxon A, Beall G, Rohr A. Immediate hypersensitivity reactions to beta-lactam antibiotics. Ann Intern Med. 1987;107:204–15.
59. Shepherd G, Burton D. Administration of cephalosporin antibiotics to patients with a history of penicillin allergy. J Allergy Clin Immunol. 1993;91:262.
60. Stewart G. Hypersensitivity and toxicity of beta-lactam antibiotics. Postgrad Med J. 1967;43(suppl 43):31–6.
61. Walters E, Romansky M, Johnson A. Cephalothin-laboratory and clinic studies in 109 patients. Antimicrob Agents Chemother. 1963:161:247–53.
62. Weinstein L, Kaplan K, Chang T. Treatment of infections in man with cephalothin. JAMA. 1964;189:829–34.
63. Hasdenteufel F, Luyasu S, Renaudin JM, et al. Anaphylactic shock associated with cefuroxime axetil: structure-activity relationships. Ann Pharmacother. 2007;41:1069–72.
64. Trcka J, Seitz CS, Bröcker EB, et al. Aminopenicillin-induced exanthema allows treatment with certain cephalosporins or phenoxymethyl penicillin. J Antimicrob Chemother. 2007;60:107–11.
65. Apter AJ, Kinman JL, Bilker WB, et al. Is there cross-reactivity between penicillins and cephalosporins? Am J Med. 2006;119:254.e11–19.
66. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol. 2005;115(3 suppl):S483–523.
67. Simons FE, Frew AJ, Ansotequi IJ, et al. Risk assessment in anaphylaxis: current and future approaches. J Allergy Clin Immunol. 2007;120(1 suppl):S2–24.